

## REMARKS

Reconsideration and allowance are respectfully requested.

Claims 18-19 are pending. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. No new issues are raised by the amendments, which merely incorporate limitations previously presented in claims 1 and 10 from which claims 18-19 used to depend. The unit dose form of claims 18-19 is a 50 µg or 100 µg tablet, which refers to the amount of active ingredient per unit dose form (see page 4, line 27, of the specification). These are nominative amounts because a "50 µg tablet" actually contains 0.0425-0.0575 mg levothyroxine sodium (based on page 4, line 29, of the specification) and a "100 µg tablet" actually contains 0.085-0.115 mg levothyroxine sodium (based on page 4, lines 31-32, of the specification). Thus, no additional search or consideration by the Examiner is required for the proposed amendments. Their entry will reduce the issues on appeal as discussed below.

### *35 U.S.C. 112 – Written Description*

Claim 21 was rejected under Section 112, first paragraph. The withdrawal of this written description rejection is requested because cancellation of claim 21 moots the Examiner's objection to the specification.

### *35 U.S.C. 103 – Nonobviousness*

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See *id.* ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by

the patent at issue"). The use of hindsight reasoning is impermissible. See *id.* at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning"). Thus, a *prima facie* case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. A claim directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* Finally, a determination of *prima facie* obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-11, 18-29 and 33-34 were rejected under Section 103(a) as allegedly unpatentable over MITRA (US 5,955,105) as evidenced by HANDBOOK (*Handbook of Pharmaceutical Excipients*, 5th Ed., pp. 134, 725 and 731-732, 2006) and MSDS (Material Safety Data Sheet, L-Thyroxine, sodium salt) in view of EUROPEAN PHARMACOPOEIA (pp. 1438 and 2002) and FRANZ et al. (US 2003/0032675). Applicants traverse.

Applicants' claims 18-19 are directed to pharmaceutical formulations in unit dose form and containing specific amounts of their components. They all require microcrystalline cellulose which has a mean particle size of less than 125 µm. Cf. Independent claim 1 previously recited the latter limitation; claims 18-19 depended from claim 1 and incorporated this limitation. A mean particle size of less than 125 µm limitation is now explicitly recited in the presently amended claims 18-19.

Claims 18-19 require, as a component of the formulation, microcrystalline cellulose having a mean particle size of less than 125 µm. Applicants have shown in their specification (Example 2) that this limitation confers the advantage of stabilizing their claimed formulations in (B) on pages 7 and 9, where the effect of microcrystalline cellulose particles size on levothyroxine sodium tablets was analyzed: "The data shows (sic) that a higher levothyroxine sodium content is maintained and the total impurities are lower when microcrystalline cellulose with a mean particle size of 50 µm or 100 µm compared to 180 µm is used in the levothyroxine sodium formulation" (page 7, lines 33-35, of the specification). Therefore, the aforementioned limitation requiring microcrystalline cellulose having a mean particle size of less than 125 µm provides the unexpected

results of maintaining higher levothyroxine sodium content and lowering the total impurities for the claimed pharmaceutical formulations. These advantages were not taught or suggested in the prior art.

MITRA discloses stabilized pharmaceutical preparations containing levothyroxine sodium. Stabilization was achieved using a water-soluble glucose polymer (e.g., maltodextrins at column 4, lines 15-16), and a partially soluble or insoluble cellulose polymer (see claim 1). Example 10 of MITRA used microcrystalline cellulose as partially soluble or insoluble glucose polymer, and starch as water-soluble glucose polymer. But MITRA is silent on the advantage of requiring the microcrystalline cellulose to have a mean particle size of less than 125  $\mu\text{m}$ , which is a requirement of the pending claims even if the proposed amendments are not entered.

Applicants' claimed invention requires microcrystalline cellulose having a mean particle size of less than 125  $\mu\text{m}$ , which was demonstrated to have certain advantages. These advantages of maintaining a higher levothyroxine sodium content and lowering the total impurities were not taught or suggested in the prior art, nor would they have been obvious to one of ordinary skill in the art with a reasonable expectation of success. Further, optimization of mean particle size to increase stability of a levothyroxine formulation was not taught or suggested by the evidence of record.

The failure of MITRA to disclose the claimed invention is not remedied by the Examiner's attempt to combine its disclosure with MSDS, EUROPEAN PHARMACOPOEIA, and FRANZ. Applicants' claims differ from what is disclosed by requiring the microcrystalline cellulose to have a mean particle size of less than 125  $\mu\text{m}$ . Neither MSDS nor EUROPEAN PHARMACOPOEIA is relevant to microcrystalline cellulose and its mean particle size. FRANZ discloses formulations containing microcrystalline cellulose but, like MITRA, the '675 application is silent on any relationship between mean particle size and stability. For example, "Sifting segregation can occur with a mean particle size in the 50 micron range and can become a dominant segregation mechanism if the mean particle size is above 100 microns" (paragraph [0033]) does not make obvious a mean particle size of less than 125  $\mu\text{m}$  for microcrystalline cellulose. In fact, it teaches away the mean particle sizes of 50  $\mu\text{m}$  and 100  $\mu\text{m}$  that were successfully used

in Applicants' Example 2. Moreover, Applicants' data show that a mean particle size of less than 125  $\mu\text{m}$  is critical for stabilizing their claimed pharmaceutical formulation. It is not the expected outcome of routine optimization.

Further experiments have been performed that were not in Applicants' specification. They evaluate the effects of changing the carrier on stability. A triturate composition of 2.5% w/w levothyroxine sodium in the carrier is selected. Microcrystalline cellulose of various mean particle sizes are evaluated for their suitability as carriers. These data confirm the results shown in Example 2 of Applicants' specification.

Triturates samples are prepared and stored under conditions of 60°C/ambient humidity and 40°C/75% RH for 14 days. The samples are assessed for stability (assay of levothyroxine sodium) and content uniformity of active ingredient (sampled in earlier fixed places). All content uniformity results and stability results are summarized in the following Tables 1 to 7.

Table 1. Batch 010201RB – carrier Cellulose Microcrystalline grade 101

| Sample  | Levothyroxine sodium content in % (% of declaration value) | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity |
|---------|--|---|---|
| 1       | 2.46 (98.4)  | 2.38  | 2.38  |
| 2       | 2.39 (95.6)  | 2.39  | 2.33  |
| 3       | 2.41 (96.4)  |   |   |
| 4       | 2.41 (96.4)  |   |   |
| 5       | 2.40 (96.0)  |   |   |
| 6       | 2.42 (96.8)  |   |   |
| Mean    | <b>2.42 (96.8)</b>   | <b>2.38 (98.5)</b>  | <b>2.35 (97.2)</b>  |
| RSD (%) | <b>1.0</b>   |   |   |

Table 2. Batch 050401RB – carrier Cellulose Microcrystalline grade 101

| Sample  | Levothyroxine sodium content in % (% of declaration value) | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity |
|---------|--|---|---|
| 1       | 2.55 (102.0)   | 2.35  | 2.35  |
| 2       | 2.47 (98.8)  | 2.39  | 2.39  |
| 3       | 2.46 (98.4)  |   |   |
| 4       | 2.44 (97.6)  |   |   |
| 5       | 2.43 (97.2)  |   |   |
| 6       | 2.47 (98.8)  |   |   |
| Mean    | <b>2.47 (98.8)</b>   | <b>2.37 (95.9)</b>  | <b>2.37 (95.9)</b>  |
| RSD (%) | <b>1.66</b>  |   |   |

Table 3. Batch 030401RB – carrier Cellulose Microcrystalline grade 102

| Sample  | Levothyroxine sodium content in % (% of declaration value) | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity |
|---------|--|---|---|
| 1       | 2.68 (107.2)   | 2.46  | 2.38  |
| 2       | 2.52 (100.8)   | 2.48  | 2.42  |
| 3       | 2.52 (100.8)   |   |   |
| 4       | 2.52 (100.8)   |   |   |
| 5       | 2.52 (100.8)   |   |   |
| 6       | 2.56 (102.4)   |   |   |
| Mean    | <b>2.55 (102.0)</b>  | <b>2.47 (96.7)</b>  | <b>2.40 (94.2)</b>  |
| RSD (%) | <b>2.56</b>  |   |   |

Table 4. Batch 040401RB – carrier Cellulose Microcrystalline grade 102

| Sample  | Levothyroxine sodium content in % (% of declaration value) | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity |
|---------|--|---|---|
| 1       | 2.60 (104.0)   | 2.52  | 2.41  |
| 2       | 2.59 (103.6)   | 2.48  | 2.40  |
| 3       | 2.55 (102.0)   |   |   |
| 4       | 2.56 (102.4)   |   |   |
| 5       | 2.62 (104.8)   |   |   |
| 6       | 2.58 (103.2)   |   |   |
| Mean    | <b>2.58 (103.2)</b>  | <b>2.50 (96.9)</b>  | <b>2.40 (93.2)</b>  |
| RSD (%) | <b>0.98</b>  |   |   |

Table 5. Batch 010701RB – carrier Cellulose Microcrystalline grade 103

| Sample  | Levothyroxine sodium content in % (% of declaration value) | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity |
|---------|--|---|---|
| 1       | 2.49 (99.6)  | 2.38  | 2.27  |
| 2       | 2.36 (94.4)  | 2.36  | 2.31  |
| 3       | 2.45 (98.0)  |   |   |
| 4       | 2.48 (99.2)  |   |   |
| 5       | 2.50 (100.0)   |   |   |
| 6       | 2.47 (98.8)  |   |   |
| Mean    | <b>2.46 (98.4)</b>   | <b>2.37 (96.3)</b>  | <b>2.29 (93.1)</b>  |
| RSD (%) | <b>2.05</b>  |   |   |

Table 6. Batch 010401RB – carrier Cellulose Microcrystalline grade 200

| Sample  | Levothyroxine sodium content in % (% of declaration value) | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity |
|---------|--|---|---|
| 1       | 2.70 (108.0)   | 2.26  | 2.33  |
| 2       | 2.75 (110.0)   | 2.26  | 2.23  |
| 3       | 2.63 (105.2)   |   |   |
| 4       | 2.63 (105.2)   |   |   |
| 5       | 2.65 (106.0)   |   |   |
| 6       | 2.61 (104.4)   |   |   |
| Mean    | <b>2.66 (106.4)</b>  | <b>2.26 (84.9)</b>  | <b>2.28 (85.7)</b>  |
| RSD (%) | <b>1.95</b>  |   |   |

Table 7. Batch 020401RB – carrier Cellulose Microcrystalline grade 200

| Sample  | Levothyroxine sodium content in % (% of declaration value) | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 40°C/75% RH | Levothyroxine sodium content in % (% of initial value) after 14 days storage in 60°C/ambient humidity |
|---------|--|---|---|
| 1       | 2.56 (102.4)   | 2.29  | 2.22  |
| 2       | 2.41 (96.4)  | 2.36  | 2.13  |
| 3       | 2.45 (98.0)  |   |   |
| 4       | 2.64 (105.6)   |   |   |
| 5       | 2.52 (100.8)   |   |   |
| 6       | 2.51 (100.4)   |   |   |
| Mean    | <b>2.51 (100.4)</b>  | <b>2.33 (92.5)</b>  | <b>2.18 (86.5)</b>  |
| RSD (%) | <b>3.27</b>  |   |   |

Note microcrystalline cellulose Grades 101, 102 and 103 have a mean particle size of 50-100 µm while microcrystalline cellulose Grade 200 has a mean particle size of 180 µm. The above results reinforce the improved stability of formulations containing microcrystalline cellulose having a mean particle size of less than 125 µm.

One of ordinary skill starting from a prior art formulation would not have found it obvious to limit the mean particle size of the microcrystalline cellulose and would not have a reasonable expectation that this change would provide the surprising result that the modified formulation maintains a higher levothyroxine sodium content and lowers the total impurities.

In summary, the cited documents fail to make obvious Applicants' claimed pharmaceutical formulations. In particular, no evidence was presented in the Office Actions that one of ordinary skill in the art would have limited the mean particle size of microcrystalline cellulose with a reasonable expectation that the formulations' stability would be improved. Therefore, Applicants' claimed invention would not have been obvious from the cited documents.

Finally, claims 18-19 require additional limitations to specific amounts of levothyroxine sodium, microcrystalline cellulose having a mean particle size of less than 125  $\mu\text{m}$ , pregelatinized starch produced by subjecting moistened starch to mechanical pressure in order to rupture some or all of its starch granules and subsequent drying, talc, colloidal anhydrous silica, and magnesium stearate. This is an independent basis for patentability from the stabilizing effect of microcrystalline cellulose having a mean particle size of less than 125  $\mu\text{m}$ .

There were no findings in the final Office Action that would be relevant to these specific amounts. In this respect, only MITRA discloses specific preparation containing levothyroxine sodium but they appear to be only the following unit dose forms: 25  $\mu\text{g}$ , 100 mg and 300 mg of the active ingredient. No unit dose forms of the required 0.0425-0.0575 mg ("50  $\mu\text{g}$  tablet") or 0.085-0.115 mg ("100  $\mu\text{g}$  tablet") levothyroxine sodium are taught or suggested. Therefore, claims 18-19 would not have been obvious from MITRA in view of MSDS, EUROPEAN PHARMACOPOEIA, and FRANZ.

For the reasons explained above, it is submitted that the claimed invention is not obvious over the cited documents. The limitation of the pending claims to microcrystalline cellulose having a mean particle size of less than 125  $\mu\text{m}$  is sufficient to distinguish over the cited documents so other incorrect allegations about their disclosures are not disputed here, but the opportunity to dispute them in the future is reserved.



Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.

*Conclusion*

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

By:                     /Gary R. Tanigawa/

Gary R. Tanigawa  
Reg. No. 43,180

901 North Glebe Road, 11th Floor  
Arlington, VA 22203-1808  
Telephone: (703) 816-4000  
Facsimile: (703) 816-4100